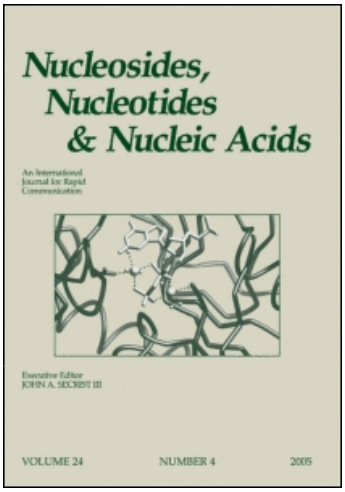

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1', 2'-*Seco*-2',3'-Dideoxynucleoside Analogues: Synthesis and Antiviral Evaluation of Racemic Trans-[1', 5'-Dihydroxy 3', 4'-methylenylpent-2'-oxy)methyl] Nucleosides

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1', 2'-*SECO*-2',3'-DIDEOXYNUCLEOSIDE ANALOGUES: SYNTHESIS AND ANTIVIRAL EVALUATION OF RACEMIC *TRANS*-[(1',5'-DIHYDROXY 3',4'-METHYLENYL-PENT-2'-OXY)METHYL] NUCLEOSIDES

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Abstract: Reaction of (±)but-3-en-1,2-diol (**3**) with ethyl diazoacetate afforded two cyclopropyl compounds (**5**) and (**6**). Their relative *trans* stereochemistry at C-2 and C-3 has been determined by high-field and computational NMR spectroscopy. (±)*Trans*-1-(1',5'-dihydroxy-3',4'-methylenyl-pent-2'-oxy)methyl]thymine (**1d**) or -cytosine (**1b**) and (±)*trans*-9-(1',5'-dihydroxy-3',4'-methylenylpent-2'-oxy)-methyl]adenine (**1a**) or -guanine (**1c**) have been obtained through a regiospecific alkylation procedure and their antiviral evaluation is reported.

Introduction

The potent antiviral activities of some acyclonucleosides such as acyclovir has generated much interest and extensive research in the synthesis of congeners bearing various side chains and aglycones.[1-5]

As part of our work concerning the synthesis of acyclic nucleosidic[6] structures with potential antiviral and antiretroviral activities, we prepared a series of acyclonucleosides (**1**) which incorporates an hydroxymethyl cyclopropyl moiety.

Very few cyclopropano nucleosides such as (**2**)[7] have been so far described[8-11] and evaluated for antiviral activity.

Results and discussion

Since degradation occured during attemps to introduce a cyclopropyl ring by modification of unsaturated acyclonucleosides,[6] the racemic acyclonucleosides (**1a-d**) were prepared by reaction of the nucleic acid base with an alkylating agent containing the cyclopropyl moiety.

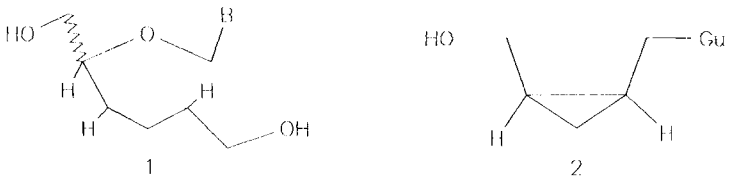


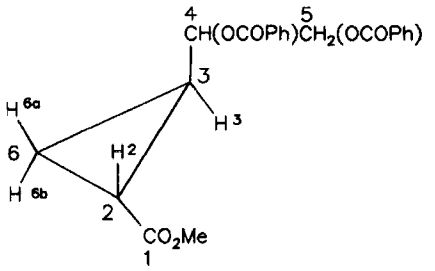
Figure- B= Ad, Cy, Gu, Th

The known[12] racemic diol (**3**) was benzoylated (scheme) to give compound (**4**) which was reacted with ethyl diazoacetate in the presence of a catalytic amount of cupric sulfate[13] at 112°C. Two new compounds were obtained after work-up and removal of diethyl fumarate and maleate by distillation under reduced pressure; their purification was achieved by a column chromatography on silica gel giving (**5**) and (**6**) in 24 and 13 % yield respectively.

Elucidation of the stereochemistry of (**5**) and (**6**) from their ^1H nmr spectra was not possible because the signal for the cyclopropyl protons was partially concealed by the resonance of the ethyl ester methyl group. The stereochemistry of these products (**5** and **6**) was therefore determined from examination of the di-O-benzoyl derivatives (**9** and **10**) of the corresponding methyl esters (**7** and **8**).

A 250 MHz ^1H NMR spectra showed for the two compounds (**9**) and (**10**) a close similarity, *i.e.* three complex multiplets near 1.6 ppm (2H, H_{6a} and H_{6b}), 2.3 ppm (2H, H_2 and H_3), and 5.1 ppm (2H, H_{5a} and H_{5b}), and a double quartet at 5.5 ppm (1H, H_4). A decoupling experiment carried out on H_4 of (**10**) (5.51 ppm) showed that H_2 is downfield to H_3 in the multiplet at 2.3 ppm. As the coupling constant $J_{3\text{-}4}$ can be extracted from the H_4 signal by first-order analysis, two simulations have been performed by taking in account the *cis* or *trans* relationships of the cyclo-

Table- Chemical Shifts (ppm/TMS) and Coupling Constants (Hz) of Compounds (**9**) and (**10**) in Acetone-d_6 obtained from Iterative Calculations; (a) The sign of this coupling constant has not been determined.

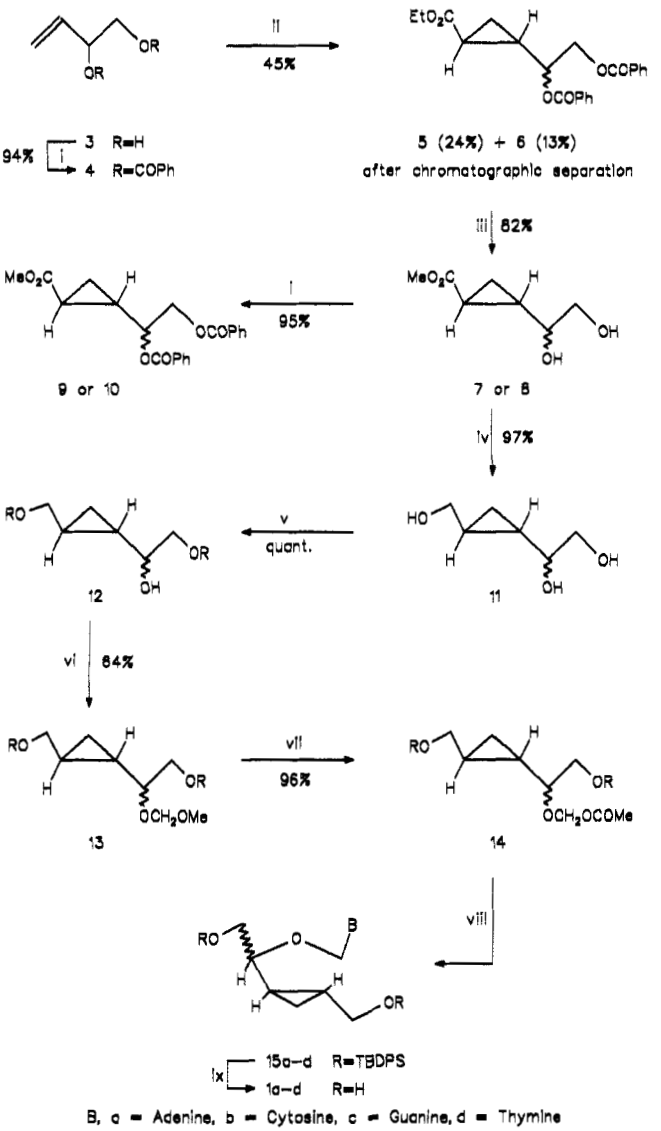


	(**9**)	(**10**)		(**9**)	(**10**)
δ_2	2.345	2.377	$J_{2\text{-}6a}$	8.5	8.5
δ_{6a}	1.630	1.614	$J_{2\text{-}6b}$	4.6	5.0
δ_{6b}	1.579	1.627	$J_{2\text{-}3}$	4.1	4.1
δ_3	2.282	2.314	$J_{6a\text{-}6b}$	-4.5	-4.5
δ_4	5.521	5.511	$J_{6a\text{-}3}$	6.3	6.2
δ_{5a}	5.095	5.130	$J_{6b\text{-}3}$	8.8	9.1
δ_{5b}	5.034	5.047	$J_{3\text{-}4}$	8.2	8.1
CO_2Me	4.005	3.976	$J_{4\text{-}5a}$	3.8	3.3
			$J_{4\text{-}5b}$	6.6	6.6
			$J_{5a\text{-}5b}$	-11.8(a)	-11.9(a)

propyl substituents in (**10**). It is known[14] that the Karplus model for H-H vicinal coupling constants is still verified in cyclopropane series and that J_{cis} is generally greater than J_{trans}.

Furthermore, geminal coupling constants are in absolute value lower than those encountered in less strained cycles. Thus, an iterative computation confirmed the *trans* relationship between H_2 and H_3 in (**10**) and gave the parameters described in Table.

The first hypothesis we considered for the stereochemistry of compound (**9**) was a *cis* relationship for the two cyclopropyl substituents, but no convergence was reached which involved parameters according to this hypothesis. In fact a 500 MHz spectrum from which parameters have



Scheme - (**5**→**7**→**9** and **6**→**8**→**10**); i, PhCOCl, pyr; ii, N_2CHCO_2Et, $CuSO_4$, 112°C; iii, MeONa, MeOH; *The following sequence was performed only from* **7**: iv, $NaBH_4$, Bu^tOH, MeOH, reflux; v, Bu^tPh_2SiCl, pyr; vi, $CH_2(OMe)_2$, P_2O_5, $CHCl_3$; vii, $BF_3.Et_2O$, Ac_2O; viii, B-$[SiMe_3]_n$, KI, 18-crown-6, PhMe, MeCN, reflux; ix, TBAF/THF; a: B=Ad; b: B=Cy; c: B=Gu; d: B=Th.

been extracted by first-order analysis, showed that in this compound too, H_2 and H_3 are in a *trans* relationship as for compound (**10**). The calculated spectra were in accordance with the experimental ones at 500 and 250 MHz as well.

The results of the nmr study point out that (**9**) and (**10**) are diastereoisomers and that the cyclopropanation of (**4**) occured in a *trans* stereospecific pathway. Our first target was directed towards the synthesis of nucleosides not paying attention at first sight to the relative configuration at C_3-C_4 of the two diastereoisomers as we were first interested on their biological behaviour. This stereochemistry is connected to that of D and L-2'-hydroxymethylaldopentonucleosides open-chain analogs. If nucleosides (**1a-d**) obtained from diastereomerically pure synthon (**7**) exhibited any antiviral activity then it would be valuable to synthesize the other series starting from (**8**) and to determine the aforementioned relative stereochemistry.

Since the direct reduction of triester (**5**) gave (**11**) with unsatisfactory yield, the subsequent reactions sequence (scheme) started with the compound (**7**). This later derivative was reduced quantitatively by $NaBH_4$ into the desired triol (**11**). The two primary alcohols were protected by the *tert*-butyldiphenylsilyl group to give (**12**) which was reacted with formaldehyde dimethyl acetal and phosphorus pentoxide to give (**13**) followed by treatment with acetic anhydride and boron trifluoride etherate[15] to afford (**14**). The compound (**14**) was the required synthon used in our condensation procedure[16] with the four trimethylsilylated nucleobases, (*i.e.* adenine, cytosine, guanine, thymine), by way of a solid-liquid phase transfer catalysis method with KI and dibenzo-18-crown-6-ether in toluene-acetonitrile (1:1 v/v). In this way, the expected regiospecific N-1 pyrimidyl and N-9 purinyl acyclic nucleosides (**15a-d**) were produced in good yields. Removal of the TBDPS groups was done by tetrabutylammonium fluoride in THF and recrystallization when possible of the crude products gave the fully deprotected nucleoside analogs (**1a-d**) (95%). The regioisomerism of the four compounds was ascertained by means of their UV spectra in two different media.[17]

None of the four acyclic nucleosides (**1a-d**) had any effect against various DNA and RNA viruses in cell cultures.

Experimental

Melting points were obtained with a Büchi (capillary) apparatus and were uncorrected. UV spectra were determined on a Cary 1186 spectrophotometer. Elemental analyses were performed by the "Service de Microanalyse du CNRS, Division de Vernaison". Mass spectra were obtained with a Jeol JMS-DX300 by the FAB ionization method. NMR spectra were recorded essentially at the "Laboratoire de Mesures Physiques de l'Université Montpellier II" on Varian EM-390, Bruker AC-250 and Bruker AM 300 spectrometers working at 90, 250.134 and 300.133 MHz respectively. Compounds were dissolved in $CDCl_3$ or DMSO-d_6 depending on their solubility, except for (**9**) and (**10**) which have been studied in Acetone-d_6 as the low viscosity of this solvent lead to the best high-resolution spectra. Simulations and iterative calculations, involving non-first-order spectra of (**9**) and (**10**) (recorded at 250.134 MHz with a digital resolution of 0.076 Hz), were performed using the Bruker PANIC software. 500 MHz spectra of (**9**) and (**10**) have been recorded on a Bruker AM-500 spectrometer (Plant Research Centre, Agriculture Canada, Ottawa, Canada) and we thank Dr. Barbara Blackwell for her kind support.

(±)1,2-Dibenzoyloxybut-3-ene (**4**).-To a solution of (±)-but-3-en-1,2-diol (**3**) (7g, 79 mmol) in anhydrous pyridine (35 ml) was added dropwise and under stirring benzoyl chloride (27.6 cm^3, 238 mmol) at 0°C. The solution was stirred at room temperature for 1h then neutralized by saturated aqueous $NaHCO_3$ and extracted with dichloromethane (200 ml). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was flash chromatographed on a silica gel column eluted with diethyl ether-cyclohexane (2:98) and afforded pure *title compound* (22g, 94% yield) as an oil; R_f 0.32 (diethyl ether-cyclohexane 2:98); ^1H NMR (90 MHz; $CDCl_3$) δ 4.52 (m, 2H, CH_2), 5.12-5.6 (m, 4H, $CH{=}CH_2$, CH), 7.08-8.12 (m, 10H, aromatic). Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.91; H, 5.38.

*(±)*trans-*Ethyl-(4,5-dibenzoyloxy-2,3-methylenyl) pentanoate* (**5**) and (**6**).-To a mixture of (**4**) (5.7g, 0.194 mmol) and copper II sulphate (0.23g) was added dropwise ethyl diazoacetate (20g, 175 mmol) at 112°C. After beeing

stirred at this temperature for 7h, the mixture was cooled at room temperature and extracted with diethyl ether (300 ml); the supernatant was decanted and the solvent evaporated under reduced pressure. Ethyl maleate and fumarate were discarded from the reaction mixture by distillation under reduced pressure (100°C, 4 mbar). The residue was chromatographed on a silica gel column using diethyl ether-cyclohexane as the eluting system. Compound (**5**) was obtained (1.8g, 24% yield) with the eluting mixture (4:96); R_f 0.36 (diethyl ether-cyclohexane 3:7); m.p. 73-74°C (cyclohexane); ^1H NMR (250 MHz; $CDCl_3$) δ 1.17-1.32 (m, 5H, H-6a, H-6b, Me), 1.70-2.00 (m, 2H, H-2, H-3), 4.16 (m, 2H, CO_2CH_2), 4.60 (m, 2H, CH_2OBz), 5.11 (m, 1H, CHOBz), 7.37-7.59 (m, 6H, aromatic), 8.02 (m, 4H, aromatic). Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.09; H, 5.79. Found: C, 69.26; H, 5.75.

Compound (**6**) (0.97g, 13% yield) was obtained as an oil by using the aforementioned eluting system (6:94); R_f 0.3 (diethyl ether-cyclohexane, 3:7); ^1H NMR (250 MHz; $CDCl_3$) δ 1.00-1.4 (m, 5H, H-6a, H-6b, Me), 1.88 (m, 1H, H-3), 1.96 (m, 1H, H-2), 4.12 (m, 2H, CO_2CH_2), 4.62 (m, 2H, CH_2OBz), 5.13 (m, 1H, CHOBz), 7.37-7.59 (m, 6H, aromatic), 8.02 (m, 4H, aromatic). Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.09; H, 5.79. Found: C, 69.31; H, 5.69.

(±)trans-Methyl-(4,5-dihydroxy-2,3-methylenyl)pentanoate (**7**) and (**8**).- To a solution of (**5**) (2.9g, 7.58 mmol) in anhydrous methanol (65 ml) was added a solution of sodium methoxide (1N, 2.5 ml) at room temperature and under stirring. After 2h the solvent was removed under reduced pressure and the residue was flash chromatographed on a silica gel column with methanol-dichloromethane (3:97) as the eluting system. *The title compound* was obtained as an oil (1g, 82% yield). R_f 0.10 (methanol-dichloromethane, 5:95); ^1H NMR (300 MHz; $CDCl_3$) δ 1.00-1.4 (m, 2H, H-6a, H-6b), 1.50-1.85 (m, 2H, H-2, H-3), 2.39 (s, 2H, OH), 3.38 (m, 1H, CH), 3.66 (s, 3H, Me), 3.52-3.76 (m, 2H, OCH_2). Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.54; H, 7.73.

The same procedure as described above was applied to the compound (**6**) and afforded (**8**) as an oil. R_f 0.10 (methanol-dichloromethane 5:95); ^1H NMR (300 MHz; $CDCl_3$) δ 0.87 (m, 1H, CH_2 cyclopropyl), 1.18 (m, 1H, CH_2 cyclopropyl), 1.51 (m, 1H, H-2), 1.70 (m, 1H, H-3), 2.38 (s, 2H, OH), 3.65 (m, 3H, Me), 3.51-3.72 (m, 2H, CH_2O). Anal. Calcd. for $C_7H_{12}O_4$: C,52.49; H, 7.55. Found: C, 52.5; H, 7.67.

*(±)*trans-*Methyl-(4,5-dibenzoyloxy-2,3-methylenyl)pentanoate (9) and (10).*-To a solution of (7) (0.32g, 2 mmol) in anhydrous pyridine (5 ml) was added dropwise benzoyl chloride (0.93 ml, 8 mmol) at 0°C. The solution was stirred at room temperature overnight, neutralized with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (100 ml). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was flash chromatographed on a silica gel column and afforded (9) as an oil (0.7g, 95% yield) with diethyl ether-cyclohexane (4:96). R_f 0.34 (diethyl ether-cyclohexane, 3:7) Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.46; H, 5.47. Found: C, 68.55; H, 5.42.

The same procedure as described before was applied to (8) and afforded (10) as an oil. R_f 0.34 (diethyl ether-cyclohexane 3:97). Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.46; H, 5.47. Found: C, 68.62; H, 5.42.

*(±)*trans-*3,4-Methylenylpentan-1,2,5-triol* (11).-To a solution of (7) (1g, 6.24 mmol) and sodium borohydride (0.471g, 12.47 mmol) in anhydrous *tert*-butyl alcohol (20 ml) was added anhydrous methanol (2 ml) portionwise. The mixture was stirred under reflux for 30 h and neutralized at room temperature by 1N aqueous HCl (5 ml). After filtration on celite the filtrate was washed with ethanol 95% (3 times), the precipitate discarded by filtration and the solution evaporated under reduced pressure to give (11) as an oil (0.8g, 97% yield). R_f 0.16 (methanol-dichloromethane, 1:10). ^1H NMR (300 MHz; DMSO-d_6) δ 0.21 (m, 1H, CH_2 cyclopropyl), 0.38 (m, 1H, CH_2 cyclopropyl), 0.62 (m, 1H, H-2), 0.81 (m, 1H, H-3), 2.96 (m, 1H, CH), 3.22 (m, 2H, H-5a, H-5b), 3.32 (m, 2H, CH_2O), 3.42 (s, 1H, OH), 3.81 (t, 2H, J = 6 Hz, OH). Anal. Calcd. for $C_6H_{12}O_3$, $1.5H_2O$: C, 45.27; H, 9.49. Found: C, 45.07; H, 9.36.

*(±)*trans-*1,5-Di*-tert-*butyldiphenylsilyloxy-3,4-methylenyl-pentan-2-ol* (12).-To a solution of (11) (0.8g, 6.05 mmol) in anhydrous pyridine (20 ml) was added dropwise *tert*-butyldiphenylchlorosilane (3.5 ml, 13.92 mmol). After beeing stirred for 1h at room temperature the solvent was evaporated under reduced pressure and the residue was extracted with dichloromethane. The organic layer was washed with saturated aqueous $NaHCO_3$, water then dried ($MgSO_4$) and evaporated. Column

chromatography of the crude product on silica gel eluted with diethyl ether-cyclohexane (3:97) afforded pure *title compound* (3.6g, 98% yield). R_f 0.44 (diethyl ether-cyclohexane, 2:8); ^1H NMR (250 MHz; $CDCl_3$) δ 0.3-0.9 (m, 4H, H-2, H-3, H-6a, H-6b), 0.94 (s, 9H, 3Me), 1.05 (s, 9H, 3Me), 1.60 (s, 1H, OH), 3.06 (td, 1H, J = 3.2 Hz, J = 8.2 Hz, H-4), 3.29 (q, 1H, J = 6.7 Hz, J = 10.6 Hz, H-1a), 3.57 (m, 2H, H-1b, H-5a), 3.78 (q, 1H, J = 3.2 Hz, J = 10.2 Hz, H-5b), 7.29-7.4 (m, 12H, aromatic), 7.55-7.75 (m, 8H, aromatic). Anal. Calcd. for $C_{38}H_{48}O_3Si_2$, $0.5H_2O$: C, 73.68; H, 8.11; Si, 9.14. Found: C, 73.85; H, 7.99; Si, 9.08.

*(±)*trans-*1,5-Di*-tert-*butyldiphenylsilyloxy-3,4-methylenyl-2-methoxy-methylenoxypentane* (13).-To a solution of (12) (1.7g, 2.89 mmol) in anhydrous chloroform (20 ml) and formaldehyde dimethyl acetal (1.07 ml, 12 mmol) was added phosphorus pentoxide (0.85g, 6 mmol) portionwise under vigorous stirring and the temperature was maintained at 40-45°C for 45 min. The reaction mixture was hydrolyzed with ice-water then neutralized by aqueous saturated $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was flash chromatographed on a column of silica gel with diethyl ether-cyclohexane (2:98) as the eluting system and afforded (13) (1.2g, 64% yield) as an oil. R_f 0.62 (diethyl ether-cyclohexane, 15:85); ^1H NMR (250 MHz; $CDCl_3$) δ 0.4-0.9 (m, 4H, H-2, H-3, H-6a, H-6b), 0.94 (s, 9H, 3Me), 1.03 (s, 9H, 3Me), 3.10 (m, 1H, H-4), 3.37 (s, 3H, OMe), 3.32-3.43 (m, 1H, H-1a), 3.55 (q, 1H, J = 5.6 Hz, J = 10.6 Hz, H-1b), 3.76 (m, 2H, H-5a, H-5b), 4.77 (m, 2H, OCH_2O), 7.3-7.39 (m, 12H, aromatic), 7.55-7.69 (m, 8H, aromatic). Anal. Calcd. for $C_{40}H_{52}O_4Si_2$: C, 73.57; H, 8.02; Si, 8.60. Found: C, 73.88; H, 8.31; Si, 8.89.

*(±)*trans-*1,5-Di*-tert-*butyldiphenylsilyloxy-3,4-methylenyl-2-acetoxy-methylenoxypentane* (14).-A solution of (13) (1.1g, 1.68 mmol) in anhydrous diethyl ether and acetic anhydride (0.23 ml, 2.43 mmol) was stirred at -20°C. To this solution was added boron trifluoride diethyl ether (0.063 ml, 0.5 mmol) dropwise. This mixture was stirred at 4°C for 20 h and then was poured in ice-water, neutralized with saturated aqueous $NaHCO_3$ and extracted with diethyl ether (2x75 ml). The etheral extracts were washed once with 10% aqueous $NaHCO_3$ and twice with water and

dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude oil was flash chromatographed on a silica gel column with diethyl ether-cyclohexane (2:98) as the eluting system and afforded (**14**) as an oil (1.1g, 96% yield). R_f 0.55 (diethyl ether-cyclohexane, 2:8); ^1H NMR (250 MHz; $CDCl_3$) δ 0.4-0.9 (m, 4H, H-2, H-3, H-6a, H-6b), 0.95 (s, 9H, 3Me), 1.05 (s, 9H, 3Me), 2.04 (s, 3H, MeCO), 3.17 (m, 1H, H-4), 3.34 (q, 1H, J = 6.5 Hz, J = 10.5 Hz, H-1a), 3.59 (q, 1H, J = 5.4 Hz, J = 10.5 Hz, H-1b), 3.75 (m, 2H, H-5a, H-5b), 5.35 (d, 1H, J = 6.3 Hz, OCHaO), 5.47 (d, 1H, J = 6.3 Hz OCHbO), 7.30-7.40 (m, 12H, aromatic), 7.55-7.69 (m, 8H, aromatic). Anal. Calcd. for $C_{41}H_{52}O_5Si_2$, $0.5H_2O$: C, 71.36; H, 7.74. Found: C, 71.13; H, 7.81.

Preparation of nucleosides **15a-d**: *General procedure.*

Silylation of nucleobases. Unprotected nucleobase (Ad, Cy, Gu, Th) (6 mmol) in hexamethyldisilazane (25 ml) and a catalytic amount of ammonium sulphate were refluxed for 1 d in the case of pyrimidines and for 2 d in the case of purines. The reagent was cautiously removed under reduced pressure.

PTC glycosylation. A solution of (**14**) and of the silylated nucleobase (1.2 mmol) in dry acetonitrile-toluene (1/1 v/v; 10 ml) containing dibenzo-18-crown-6-ether (0.2 mmol) and potassium iodide (0.8 mmol) was stirred for 1 h in the case of pyrimidines and 2 h in the case of purines at 80°C under an atmosphere of dry argon. The insoluble material was filtered off and the filtrate evaporated under reduced pressure. The residue was chromatographed on a silica gel column using methanol-dichloromethane as the eluting system.

*(±)trans-9-[(1,5-Di-*tert*-butyldiphenylsilyloxy-but-3,4-methylenylpent-2-oxy)methyl]adenine* (**15a**).-The *title compound* was obtained as an oil following the aforementioned procedure and after chromathography with methanol-dichloromethane (3:97) as the eluting system (0.415g, 55% yield). R_f 0.31 (methanol-dichloromethane, 3:97); UV λ_{max}(EtOH, 95%) 258 nm (ϵ 13100); ^1H NMR (250 MHz; $CDCl_3$) δ 0.3 (m, 2H, cyclopropyl), 0.63 (m, 2H, cyclopropyl), 0.91 (s, 9H, 3Me), 1.01 (s, 9H, 3Me), 3.10 (m, 1H, H-4), 3.21 (q, 1H, J = 6.2 Hz, J = 10.5 Hz, H-1a), 3.51 (q, 1H, J = 5.0 Hz, J = 10.5 Hz, H-1b), 3.78 (m, 2H, H-5a, H-5b), 5.74 (s, 2H, NCH_2O), 6.64 (s, 2H, NH_2), 7.28-7.65 (m, 20H, aromatic),

7.92 (s, 1H, H-2), 8.36 (s, 1H, H-8). FAB-MS (*m*-nitrobenzyl alcohol matrix): m/e 756 $(M+H)^+$, 136 $(BH+H)^+$. Anal. Calcd. for $C_{44}H_{53}N_5O_3Si_2$: C, 69.89; H, 7.07; N, 9.26. Found: C, 69.94; H, 6.89; N, 9.20.

*(±)*trans-*1-[(1,5-Di*-tert-*butyldiphenylsilyloxy-3,4-methylenylpent-2-oxy)-methyl]cytosine* (**15b**).-The *title compound* was obtained as an oil following the aforementioned procedure and after chromatography (0.69g, 95% yield) with methanol-dichloromethane (3:97) as the eluting system R_f 0.46 (methanol-dichloromethane 1:9); UV λ_{max}(EtOH, 95%) 269 nm (ϵ 7700); ^1H NMR (250 MHz; $CDCl_3$) δ 0.42 (m, 1H, cyclopropyl), 0.59-0.77 (m, 3H, cyclopropyl), 0.97 (s, 9H, 3Me), 1.03 (s, 9H, 3Me), 3.08 (m, 1H, H-4), 3.2 (q, 1H, J = 10.6 Hz, J = 6.4 Hz, H-1a), 3.54 (q, 1H, J = 5.1 Hz, J = 10.6 Hz, H-1b), 3.74 (m, 2H, H-5a, H-5b), 5.33 (AB system, 2H, J = 10.3 Hz, NCH_2O), 5.55 (d, 1H, J = 7.2 Hz, H-5), 7.27-7.67 (m, 23H, NH_2, H-6, aromatic). FAB-MS (*m*-nitrobenzyl alcohol): m/e 732 $(M+H)^+$, 112 $(BH+H)^+$. Anal. Calcd. for $C_{43}H_{53}N_3O_4Si_2$: C, 70.54; H, 7.29; N, 5.74. Found: C, 70.60; H, 7.33; N, 5.65.

*(±)*trans-*9-[(1,5-Di*-tert-*butyldiphenylsilyloxy-3,4-methylenylpent-2-oxy)-methyl]guanine* (**15c**).-The *title compound* was obtained as crystals following the aforementioned procedure and after chromatography (0.69g, 90% yield) with methanol-dichloromethane (7:93) as the eluting system. R_f 0.21 (methanol-dichloromethane 8:92), m.p. 233-234°C (methanol-dichloromethane); UV λ_{max}(EtOH,95%) 252 nm (ϵ 11900); ^1H NMR (250 MHz; DMSO-d_6) δ 0.25-0.80 (m, 4H, cyclopropyl), 0.84 (s, 9H, 3Me), 0.90 (s, 9H, 3Me), 3.18-3.41 (m, 2H, H-4, H-1a), 3.54-3.72 (m, 3H, H-1b, H-5a, H-5b), 5.69 (AB system, 2H, J = 10.7 Hz, NCH_2O), 6.20 (s, 2H, NH_2), 7.33-7.59 (m, 20H, aromatic), 8.07 (s, 1H, H-8), 10.90 (s, 1H, NH). FAB-MS (*m*-nitrobenzyl alcohol): m/e 772$(M+H)^+$, 152$(BH+H)^+$. Anal. Calcd. for $C_{44}H_{53}N_5O_4Si_2$, $0.5H_2O$: C, 67.65; H, 6.96; N, 8.96. Found: C, 67.70; H, 6.85; N, 9.15.

*(±)*trans-*1-[(1,5-Di*-tert-*butyldiphenylsilyloxy-3,4-methylenylpent-2-oxy)-methyl]thymine* (**15d**).-The *title compound* was obtained as an oil following the aforementioned procedure and after chromatography with

methanol-dichloromethane (2:98) as the eluting system (0.47g, 64% yield). R_f 0.49 (methanol-dichloromethane, 1:9); UV λ_{max}(EtOH, 95%) 263 nm (ϵ 8300); ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.4-0.95 (m, 4H, cyclopropyl), 0.95 (s, 9H, 3Me), 1.02 (s, 9H, 3Me), 1.85 (d, 3H, J = 1.2 Hz, Me), 3.14 (m, 1H, H-4), 3.31 (m, 1H, H-1a), 3.44 (m, 1H, H-1b), 3.72 (m, 2H, H-5a, H-5b), 5.18 (AB system, 2H, J = 10.3 Hz, NCH_2O), 7.07 (d, 1H, J = 1.2Hz, H-6), 7.40 (m, 12H, aromatic), 7.66 (m, 8H, aromatic), 8.57 (s, 1H, NH). FAB-MS (*m*-nitrobenzyl alcohol): m/e 747 $(M+H)^+$, 127 $(BH+H)^+$. Anal. Calcd. for $C_{44}H_{54}N_2O_5Si_2$: C, 70.55; H, 7.27; N, 3.74. Found: C, 70.32; H, 7.20; N, 3.91.

Desilylation of nucleosides: General procedure.-To a stirred solution of silylated nucleosides (**15**) (1 mmol) in THF (2.5 ml) was added a solution (3 mmol, 0.9 ml) of tetrabutyl-ammonium fluoride (1.1 mol dm^{-3} in THF) at room temp. for 1.5 h. The solvent was evaporated under reduced pressure and the free nucleoside (1) was obtained in 95-98% yield after recrystallization or chromatography on a silica gel column.

(±)trans-9-[(1,5-Dihydroxy-3,4-methylenylpent-2-oxy)methyl]adenine(**1a**). -M.p. 163-164°C (from CH_2Cl_2); R_f 0.09 (methanol-dichloro-methane 1:9);UV λ_{max}(EtOH, 95%) 259 nm (ϵ 12800); UV λ_{max}(0.1M KOH) 259 nm; ^{1}H NMR (250 MHz; DMSO-d_6) δ 0.24 (m, 2H, cyclopropyl), 0.64 (m, 2H, cyclopropyl), 3.06-3.25 (m, 3H, H-1a, H-1b, H-4), 3.33-3.50 (m, 2H, H-5a, H-5b), 4.42 (t, 1H, J = 5.5 Hz, OH), 4.69 (t, 1H, J = 5.7 Hz, OH), 5.60 (AB system, 2H, J = 10.9 Hz, NCH_2O), 7.29 (s, 2H, NH_2), 8.15 (s, 1H, H-2), 8.24 (s, 1H, H-8); FAB-MS (thioglycerol): m/e 280 $(M+H)^+$, 136 $(BH+H)^+$. Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.13. Found: C, 51.35; H, 6.33.

(±)trans-1-[(1,5-Dihydroxy-3,4-methylenylpent-2-oxy)methyl]cytosine (**1b**).-The *title compound* was obtained as an oil after column chromatography with methanol-dichloromethane (18:82) as the eluting system. R_f 0.18 (methanol-dichloromethane 12:88); UV λ_{max}(EtOH, 95%) 268 nm (ϵ 7400); UV λ_{max}(0.1 M KOH) 281 nm; ^{1}H NMR (250 MHz; DMSO-d_6) δ 0.3-0.8 (m, 4H, cyclopropyl), 2.94 (m, 1H, H-4), 3.09-3.27 (m, 2H, H-1a, H-1b), 3.32 (m, 2H, H-5a, H-5b), 4.45 (s, 1H, OH), 4.62 (s, 1H, OH), 5.12 (AB system, 2H, J = 9.8 Hz, NCH_2O),

5.69 (d, 1H, J = 7.2 Hz, H-5), 7.15 (m, 2H, NH_2), 7.59 (d, 1H, J = 7.2 Hz, H-6). FAB-MS (thioglycerol): m/e 256 $(M+H)^+$, 112 $(BH+H)^+$. Anal. Calcd. for $C_{11}H_{17}N_3O_4$, $0.75CH_2Cl_2$: C, 44.23; H, 5.84. Found: C, 44.26; H, 6.15.

*(±)*trans-*9-[(1,5-Dihydroxy-3,4-methylenylpent2-oxy)methyl]guanine*(**1c**). -The *title compound* was obtained as an oil after column chromatography on silica gel 60 silanised eluting with water. R_f 0.54 (propan-2-ol-ammonia-water 8:1:1); UV λ_{max}(EtOH, 95%) 250 nm (ϵ 11800); UV λ_{max}(0.1M KOH) 268 nm and 264 nm *(sh)*; ^1H NMR (250 MHz; DMSO-d_6) δ 0.2-0.80 (m, 4H, cyclopropyl), 3.00-3.19 (m, 2H, H-1a, H-4), 3.40-3.53 (m, 3H, H-1a, H-5a, H-5b), 4.44 (s, 1H, OH), 4.66 (s, 1H, OH) 5.37 (AB system, 2H, J = 10.8 Hz, NCH_2O), 6.61 (s, 1H, NH_2), 7.78 (s, 1H, H-8), 10.86 (s, 1H, NH). FAB-MS (Thioglycerol): m/e 294 $(M-H)^-$, 150 $(BH-H)^-$. Anal. Calcd. for $C_{12}H_{17}N_5O_4$, $1H_2O$: C, 46.14; H, 6.13. Found: C, 45.86; H, 6.39.

*(±)*trans-*1-[(1,5-Dihydroxy-3,4-methylenylpent-2-oxy)methyl]thymine* (**1d**).-The *title compound* was obtained as an oil after column chromatography with methanol-dichloromethane (17:83) as the eluting system. R_f 0.11 (methanol-dichloromethane 1:9); UV λ_{max}(EtOH, 95%) 262 nm (ϵ 8100); UV λ_{max}(0.1MHCl) 263 nm; ^1H NMR (300 MHz; DMSO-d_6) δ 0.35-0.80 (m, 4H, cyclopropyl), 1.76 (d, 3H, J = 1.3 Hz, Me), 2.99 (m, 1H, H-4), 3.13-3.50 (m, 4H, H-1a, H-1b, H-5a, H-5b), 4.45 (t, 1H, J = 5.7 Hz, OH), 4.62 (t, 1H, J = 5.7 Hz, OH), 5.12 (AB system, 2H, J = 10.1 Hz, NCH_2O), 7.54 (d, 1H, J = 1.3 Hz, H-6), 11.27 (s, 1H, NH). FAB-MS (thioglycerol): m/e 269 $(M-H)^-$, 125 $(BH-H)^-$. Anal. Calcd. for $C_{12}H_{18}N_2O_5$: C, 53.32; H, 6.71. Found: C, 53.50; H, 6.56.

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